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Research Article

COMPARATIVE *IN SILICO* ANALYSIS OF PHYTOCONSTITUENTS FROM *MOMARDICA DIOICA, LEUCUS ASPERA* AND *ACYLPHA INDICA* ELUCIDATING FOR THE ANTIBACTERIAL ACTIVITIES

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Abstract:

Medicinal plants are the only source for the treatment of diseases in ancient days and since then numerous herbs and plants have been recognized as medicinal plants because of their potency to cure various ailments. Medicinal plants are the rich source of lead molecules for new drug discovery and hence the biological importance of medicinal plants is increasing rapidly nowadays. The present investigation deals with the *in*-screening of the phytoconstituents of *Momardica dioica*, *Leucus aspera* and *Acylpha indica* plant species against the specific targets of antimicrobial activity by using various molecular modelling tools for predicting the reasonable mechanism of action. Current study focuses on discovery of potent inhibitors for DNA Gyrase via computational methods. These components were also under the ADME toxicity level and lied in Lipinski's rules of 5 and 3. The potential unique inhibitors and predicted associations might aid in disease inhibition. There is crucial requisite for the effective drug designing of antimicrobial agents. This approach gave an insight to develop these biologically active molecules in laboratory with their synergetic effect for further animal model studies.

Key words: in-silico screening, DNA gyrase, Antimicrobial agents and Docking.

1. Introduction:

Traditional system of medicine is used throughout the world and from century's herbs have been the original source for most of the drugs. Medicinal plants contain so many chemical compounds which are the major source of

therapeutic agents to cure human disease. Recent discovery and advancement in medicinal and aromatic plants have lead to the enhancement of health care of mankind. Through the systematic evaluation of the safety and efficacy of thousands of plant metabolites are being successfully and used for the treatment of variety of ailments. 80% of the world's population relies on plants for their medication [1]. There are some plants, which are known for their historical importance for using in different ailments therapy. Momordica fruit is one of its kind used widely in southern Asia countries especially India.

Momordica genus includes 187 species of those 19 are accepted species [2-4]. *Momordica dioica* (M. dioica) is a perennial dioiceous climber creeper plant belongs to the family Cucurbitaceae, found throughout India. Folk medicinally, M. dioica is used both in the prevention and cure of various diseases [5]. *Leucas aspera* is one of the herbs found momentous due to its overriding medicinal outcomes. Many phytochemicals belong to the classes of terpenes, terpenoids, sterols and fatty compounds, glycosides, long-chain compounds, flavonoids, lignanes, alkaloids and others were identified and isolated by different extraction methods [6,7]. *Acalypha indica* Linn. (Family: Euphorbiaceae), is a small annual shrub which generally occurs as a troublesome weed in gardens, roadsides and throughout the plains of India [8]. The present investigation deals with the in silico screening of the phytoconstituents of these three plant species against the specific targets of antimicrobial activity by using various molecular modelling tools for predicting the reasonable mechanism of action.

2. Materials and methods:

2.1. Data collection

In current study, the details about the phytochemicals and their data extraction was the critical part as the information about the plant species according to their habitats and geographical distributions were important. The botanical aspects of the plants such as ethnobotany, habitat and phytochemicals for the current plant species (*M. dioica*, *L. aspera* and *A. indica*) were obtained from the Germplasm Resources Information Network (GRIN) Taxonomy for Plants [9, 10]. The data obtained from botanical sources, *in silico* and structural level studies were collected, processed and refined.

The plants species names were used as input in Dr. Duke's Phytochemical and Ethnobotanical Databases (DDPED) to retrieve the quantitative phytochemical data of respective species [11, 12]. By applying the filter of phytochemistry,

information about anti-bacterial, anti-microbial and anti-septic phytochemicals were obtained. Secondary metabolites having anti-bacterial properties were selected for further studies.

2.2. Structure retrievals:

2D structures of phytochemicals or ligands in the medicinal plants (*M. dioica*, *L. aspera* and *A. indica*) were retrieved from PubChem database [13, 14] and converted into PDB format using PyMol (https://www.pymol.org/). 3D structure of anti-bacterial target protein DNA Gyrase (PDB ID: 5CDR) was retrieved from Protein Data Bank (PDB) [15, 16].

2.3. ADMET and drug related properties:

Drug related properties and bioactivity (molecular mass, Log *P*, hydrogen bond acceptor and donors, rotatable bonds, PSA and Ro5 violations) of lead compounds were calculated by mCule suit [17, 18] and Molinspiration [19, 20]. Oral bioavailability of drug molecules can be easily predicted by value of Log *P* [21]. To analyze the Lipinski's rule of five, number of rotatable bonds, H-bond acceptors and H-bond donors were attained by utilizing mCule suit and Molinspiration. According to this rule, molecules that can easily cross the membrane have molecular weight ≤500, hydrogen bond donor's ≤5, Log P ≤5, and hydrogen bond acceptors ≤10 [22, 23]. The absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties were also analyzed by the Admet SAR server [24, 25].

2.4. Comparative molecular docking analyses:

The geometry optimization of selected phytochemicals was accomplished by Chem3D Ultra [26] and UCSF Chimera 1.5.2 [27]. Shortlisted 19 lead compounds were docked into the binding cavity of target protein DNA Gyrase through Molegro Virtual Docker (MVD) [28, 29]. The grid box of x-axis 44.05 A˚, y-axis 46.93 A˚ and z-axis of 45.08 A˚ was utilized for MVD with exhaustiveness of 8. Genetic algorithm was utilized with 100 runs with default parameters for MVD molecular docking studies. Successive analyses on carefully chosen lead compounds were carried out and comparative molecular docking analyses were performed to pinpoint the binding affinities by selected docking tools. The least binding energy and highest binding affinity complexes were designated and analyzed by UCSF Chimera 1.5.2 and LigPlot [30].

2.5. Ligand based pharmacophore generation:

To generate ligand-based pharmacophore models, scrutinized compounds from selected three species of plants were employed in the ligand-based module of the LigandScout 3.0 [31]. Pharmacophoric sites including positive and

negative ionizable groups, aromatic ring, hydrophobic sites, hydrogen bond acceptor (HBA) and hydrogen bond donor (HBD) were carefully characterized. Merge feature model generation and atom overlap scoring function of LigandScout 3.0 was applied for the incorporation of associated features of utilized compounds. Virtual screening was performed against natural products library and top pharmacophore scored (>80%) molecules were used for further analyses.

3. Results and discussion:

Data extraction was performed by applying restricted search against GRIN Taxonomy for plants database. Subsequently, geographical habitat and data retrieved through DDPED (http://www.ars-grin.gov/duke) related to phytochemicals of selected species was used as basic filter to reduce the number of hits. Antibacterial, antimicrobial phytochemicals were searched and retrieved from selected species. 26 phytochemicals were selected by database search and after removing redundancy phytochemicals were classified according to the species (Table 1).

Molecular properties such as permeability of membrane and bioavailability are always associated with partition coefficient (Log P), molecular weight, number of hydrogen bond donors and acceptors as basic molecular descriptors. Lipinski "Rule of Five" was articulated by utilizing these molecular descriptors. Therefore, Lipinski's Rule of Five was employed to estimate the bioavailability features like ADMET properties of the lead compounds and these properties were calculated by mCule tool and Molinspiration (Table 2-3). 19 out of 26 molecules strictly followed the Lipinski's Rule of five and were selected for further analyses and rest were rule out. ADMET properties of selected 19 compounds showed the potential of effective drug molecules (Table 3). 3D structures of all these selected phytochemicals were minimized for stability and for energy minimization by Chem3D Ultra and UCSF Chimera 1.5.2. The retrieved protein structure from PDB was minimized at 1000 steepest by utilized UCSF Chimera 1.5.2 for comparative molecular docking analyses of scrutinized ligands. The selected 19 compounds (Machilin C, Ascorbic-Acid, Gentisic-Acid, Lauric-Acid, Nerolidol, P-Cymene, Pectin, Rosmarinic-Acid, Squalene, Leucasperones A, Leucasperones B, Leucasperols A, Leucasperol B, Nectandrin B, Machilin G, Chicanine, Licarin A, Acalyphin) were docked with DNA Gyrase by using Molegro Virtual Docker. All the seleceted ligands showed effective binding with all the selected tools having least binding energy and highest binding affinity. The better MolDock scores was observed with Gentisic-Acid, Leucasperones B, Leucasperol B and Licarin A compound (Table 4).

All the generated complexes from all the selected tools were analyzed and visualized on minimum binding energy, inhibition constant, utmost binding affinity and drug properties. Interestingly, it was observed that all the compounds from selected utilized docking tools showed interactions Glu42, Val 43, Asn 46, Glu 50, Asp 73, Gly 77, Ile 90, Met 91, Val 120, Arg 136 and Thr 165 residues (Figures 1- 4).

Selected molecules were scanned analytically, and it was observed that most of the compounds bound in the binding domain. Molegro Virtual Docker docking analyses revealed that Glu42, Val 43, Asn 46, Glu 50, Asp 73, Gly 77, Ile 90, Met 91, Val 120, Arg 136 and Thr 165 residues are conserved residues involved in binding. The docking studies exposed that scrutinized and novel molecules bind similarly and uncovered the potential binding pocket.

Cross experiments were executed to validate the results, three different pharmacophores were also generated of each plant extracted species and screened the natural compounds library against all. Interestingly, the top screened molecules were the same that screened from the pharmacophore generated from all the species.

Current study focuses on discovery of potent inhibitors for DNA Gyrase via computational methods. The pursuit for potent inhibitors of DNA Gyrase was achieved through screening phytochemicals present in *M. dioica*, *L. aspera* and *A. indica* having antibacterial and antimicrobial properties. 26 compounds were shortlisted, and bioinformatics tools were utilized for further refining of molecules on the basis of ADMET properties resulting in identification of 19 ligands that satisfy Lipinski's rule of five.

In comparison to existing inhibitors, the binding energy values of novel inhibitors were observed least and exhibiting strong interaction with protein. The protein–ligand binding interaction has significant role in determining the action and binding likelihood of the drug.

This work introduces the significance of medicinal plants and potential target protein in the treatment of anti-inflammatory and autoimmune disease RA. Study of medicinal plants has given an understanding that natural components (Gentisic-Acid, Leucasperones B, Leucasperol B and Licarin A) of plant *M. dioica*, *L. aspera* and *A. indica* showed effective activity on docking with DNA Gyrase.

These components were also under the ADME toxicity level and lied in Lipinski's rules of 5 and 3. The potential unique inhibitors and predicted associations might aid in disease inhibition. There is crucial requisite for the effective

drug designing of antimicrobial agents. This approach gave an insight to develop these biologically active molecules in laboratory with their synergetic effect for further animal model studies.

Table 1: The Phytochemicals possessing Antimicrobial and Antibacterial Properties.

Momardica dioica	**Leucus aspera**	**Acylpha indica**
Ascorbic Acid	Leucasperones A and B	Acalyphine
β-Sitosterol	Leucasperols A and B	Ascorbic-Acid
Cycloartenol	Leucasperosides A, B and C	Kaempferol
Gentisic Acid	Nectandrin B	2-Methylanthraquinone
Lauric Acid	Machilin C	
Nerolidol	Chicanine	
P-Cymene	Licarin A	
Pectin		
Rosmarinic-Acid		
Squalene		
Verbascoside		

Table 2: Lipinski's Rule of Five screening with Molinspiration.

S. No	Phytochemical	Molecular Weight	AlogP	H-Bond Acceptor	H-Bond Donor	Rotatable Bonds	Violations
1	Machilin C	356.42	4.52	5	0	4	0
2	Ascorbic-Acid	176.12	-1.41	6	4	2	0
3	β-Sitosterol	414.72	8.02	1	1	6	1
4	Cycloartenol	426.73	8.17	1	1	4	1
5	Gentisic-Acid	154.12	0.8	3	3	1	0
6	Lauric-Acid	200.32	3.99	1	1	10	0

7	Nerolidol	222.37	4.4	1	1	7	0
8	P-Cymene	134.22	3.12	0	0	1	0
9	Pectin	194.14	-3.13	6	5	1	0
10	Rosmarinic-Acid	360.32	1.76	7	5	6	0
11	Squalene	410.73	10.6	0	0	15	0
12	Verbascoside	624.59	-1.02	15	9	10	3
13	Leucasperones A	478.58	3.45	8	1	8	0
14	Leucasperones B	436.55	2.88	7	2	7	0
15	Leucasperols A	352.47	2.43	5	2	0	0
16	Leucasperol B	352.47	2.43	5	2	0	0
17	Leucasperosides A	788.88	-2.24	17	10	10	3
18	Leucasperoside B	626.74	-0.06	12	7	7	3
19	Leucasperoside C	772.88	-1.21	16	9	9	3
20	Nectandrin B	344.41	4.2	5	2	4	0
21	Machilin G	356.42	4.52	5	0	4	0
22	Chicanine	342.39	4.21	5	1	3	0
23	Licarin A	326.39	4.68	4	1	4	0
24	Acalyphin	360.32	-3.61	10	5	4	0
25	Kaempferol	286.24	2.28	6	4	1	0
26	2-Methylanthraquinone	222.24	2.77	2	0	0	0

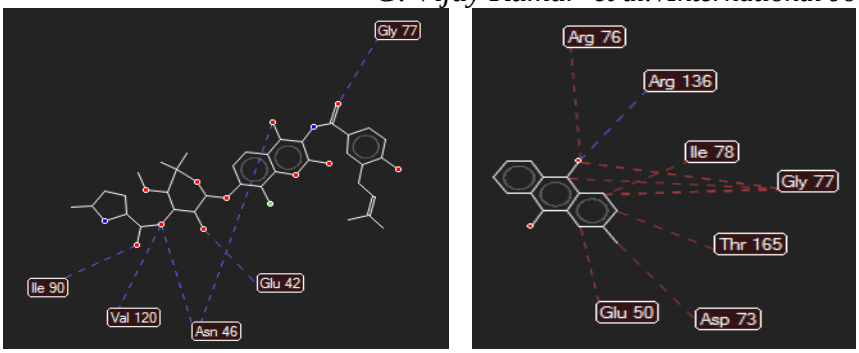
Table 3: ADMET properties prediction with mCule online server.

Phytochemical	Human Intestinal Absorption	Caco-2	Blood Brain Barrier	Human oral bioavailability	PGP inhibitior	PGP substrate	Carcino-genicity	Ames mutagenesis	Hepato-toxicity	Acute Oral Toxicity
Machilin C	+ 0.9928	+ 0.8389	+ 0.9317	- 0.6	+ 0.811	- 0.9306	- 0.9429	- 0.54	+ 0.65	III 0.6548
Ascorbic-Acid	+ 0.815	- 0.9755	+ 0.9785	+ 0.5857	- 0.9715	- 0.9682	- 0.8589	- 0.94	- 0.9	IV 0.5871
β-Sitosterol	+ 0.993	+ 0.5385	+ 0.9247	+ 0.5286	- 0.5	+ 0.827	- 0.9714	- 0.87	- 0.75	I 0.4287
Cycloartenol	+ 0.9901	+ 0.5826	+ 0.8663	- 0.5143	- 0.6207	- 0.7725	- 0.9714	- 0.88	- 0.7	III 0.7683
Gentisic-Acid	+ 0.9877	+ 0.6467	-0.935	- 0.5143	- 0.9844	- 0.9872	- 0.6371	- 0.88	- 0.625	III 0.6994
Lauric-Acid	+ 0.8417	+ 0.7507	+ 0.9725	- 0.6714	- 0.9707	- 0.9647	- 0.6571	- 1	- 0.9	IV 0.6378
Nerolidol	+ 0.9645	+ 0.8528	+ 0.989	- 0.6	- 0.9634	- 0.9445	- 0.6143	- 0.9	- 0.8	III 0.9
P-Cymene	+ 0.9905	+ 0.9388	+ 1	+ 0.9571	- 0.9805	- 0.9782	- 0.5143	- 0.9	- 0.75	III 0.8434
Pectin	- 0.9392	-0.9635	+ 0.7891	- 0.5286	- 0.9714	- 0.9969	- 0.9571	- 0.79	- 0.75	IV 0.4355
Rosmarinic-Acid	+ 0.9666	-0.9373	-0.3334	- 0.7	- 0.8529	-0.934	- 0.8578	- 0.65	+ 0.625	III 0.772
Squalene	+ 0.9206	+ 0.7004	+ 0.9962	- 0.5143	+ 0.6611	- 0.9803	+ 0.6571	- 0.97	- 0.575	III 0.8971
Verbascoside	+ 0.6642	-0.9049	-0.3799	- 0.9	- 0.5537	- 0.6291	- 0.9429	- 0.62	- 0.5	III 0.8034

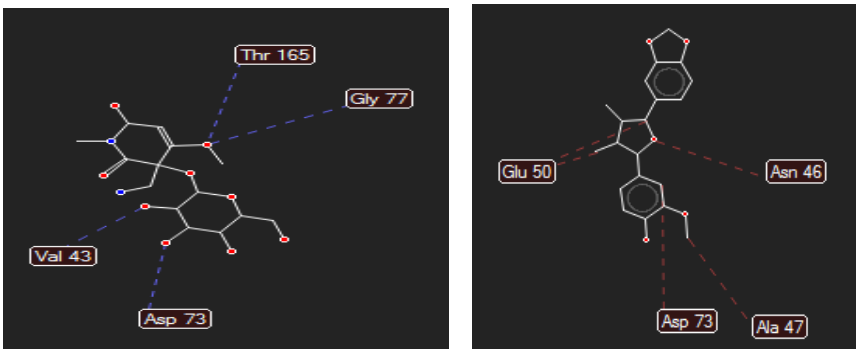
Leucasperones A	+ 0.9906	-0.5568	+ 0.9726	- 0.6714	+ 0.6979	- 0.6096	- 0.9571	- 0.64	- 0.5	III 0.7685
Leucasperones B	+ 0.9892	+ 0.5428	+ 0.8505	- 0.5714	- 0.5438	- 0.6388	- 0.9857	- 0.57	- 0.6	III 0.7519
Leucasperols A	+ 0.7919	+ 0.6229	+ 0.9754	- 0.5	- 0.8042	- 0.7567	- 1	- 0.5	- 0.7	III 0.4777
Leucasperol B	+ 0.7919	+ 0.6229	+ 0.9754	- 0.5	- 0.8042	- 0.7567	- 1	- 0.5	- 0.7	III 0.4777
Leucasperoside A	+ 0.7848	-0.8873	- 0.3042	- 0.7286	+ 0.7184	- 0.7503	- 0.9857	- 0.75	- 0.675	III 0.7826
Leucasperoside B	+ 0.7848	-0.8656	- 0.3042	- 0.7429	+ 0.6534	- 0.8362	- 0.9857	- 0.74	- 0.725	III 0.7826
Leucasperoside C	+ 0.7848	-0.8792	- 0.3042	- 0.7714	+ 0.7165	- 0.6452	- 0.9857	- 0.73	- 0.6	III 0.7826
Nectandrin B	+ 0.9965	+ 0.7708	+0.868	- 0.5714	+ 0.6068	- 0.9695	- 0.9	- 0.63	+ 0.55	III 0.6752
Machilin G	+ 0.9928	+ 0.8389	+ 0.9317	- 0.6	+ 0.811	- 0.9306	- 0.9429	- 0.54	+ 0.65	III 0.6548
Chicanine	+ 0.99	+ 0.7592	+ 0.9106	- 0.7	+ 0.6062	- 0.9625	- 0.9571	- 0.51	+ 0.575	III 0.6252
Licarin A	+ 0.9948	+ 0.8731	+ 0.8702	- 0.6429	- 0.4335	- 0.8493	- 0.8857	- 0.72	+ 0.7	III 0.5041
Acalyphin	- 0.6154	-0.7932	+ 0.8643	- 0.6286	- 0.8294	- 0.8981	- 0.9286	- 0.51	- 0.675	III 0.57
Kaempferol	+ 0.9881	-0.8637	- 0.5635	- 0.6286	- 0.8576	- 0.7327	- 1	+ 0.73	+ 0.775	II 0.6238
2-Methyl anthraquinone	+ 0.9973	+ 0.8572	+ 0.9064	+ 0.8571	- 0.815	- 0.9815	- 0.6787	+ 0.63	+ 0.85	III 0.7574

Table 4: Docking results of the selected molecules with Molegro Virtual Docker.

S. No	Phytochemical	MolDock Score	Rerank Score	H bond	Interaction	Internal	Docking score
1		-203.2	-135.3	-13.9	-190.5	-12.6	-181.5
2	Machilin C	-47.4	-13.5	-2.4	-75.7	28.3	-70.5
3	Ascorbic-Acid	-58.3	47.0	-13.4	-91.1	32.8	-88.9
4	Gentisic-Acid	-103.5	-76.5	0	-113.3	9.8	-109.3
5	Lauric-Acid	-38.9	41.5	-5.8	-48.7	9.8	-71.2
6	Nerolidol	-63.6	104.8	-12.2	-90.9	27.2	-93.8
7	P-Cymene	-78.9	-63.5	0	-74.8	-4.0	-93.2
8	Pectin	-70.1	-31.8	-6.4	-81.9	11.8	-77.2
9	Rosmarinic-Acid	-73.7	-29.1	-5.4	-84.7	10.9	-87.3
10	Squalene	-93.1	41.3	-8.0	-111.0	17.9	-95.4
11	Leucasperones A	-80.6	23.7	-4.4	-98.5	17.8	-100.9
12	Leucasperones B	-123.1	-92.6	0	-130.2	7.1	-125.9
13	Leucasperols A	-96.8	-44.6	-2.8	-105.7	8.8	-105.8
14	Leucasperol B	-105.5	28.6	-7.8	-121.1	15.5	-123.3
15	Nectandrin B	-37.6	-4.0	-2.2	-96.2	0.1	-111.6
16	Machilin G	-44.9	28.5	0	-46.1	8.5	-58.1
17	Chicanine	-100.4	4.2	-8.3	-65.8	20.9	-56.4
18	Licarin A	-100.4	-51.1	-3.3	-109.1	8.5	-129.6
19	Acalyphin	-86.9	69.9	0	-60.1	-26.8	-117.3

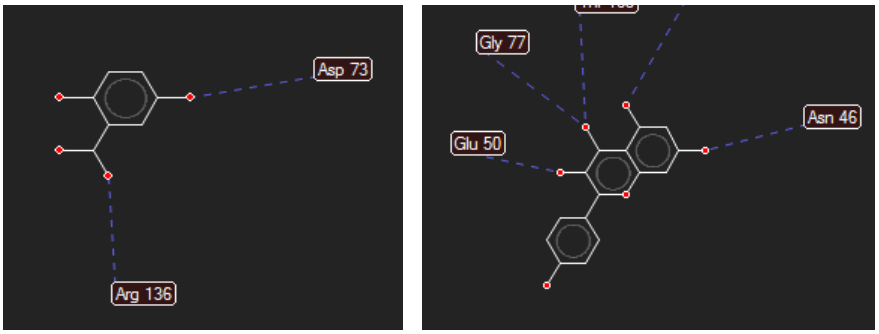


Standard (Co-Crystalized ligand) Machilin C

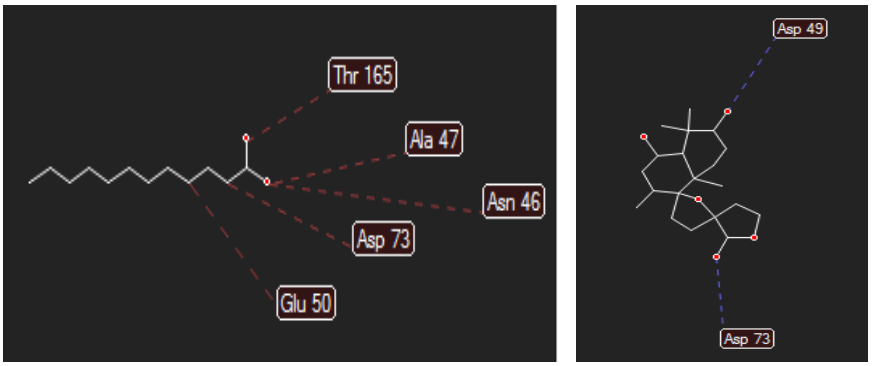


Ascorbic-Acid Gentisic-Acid

Figure 1: Binding interactions of selected molecules with DNA Gyrase-1



P-Cymene Nerolidol



Lauric-Acid Pectin

Figure 2: Binding interactions of selected molecules with DNA Gyrase-2

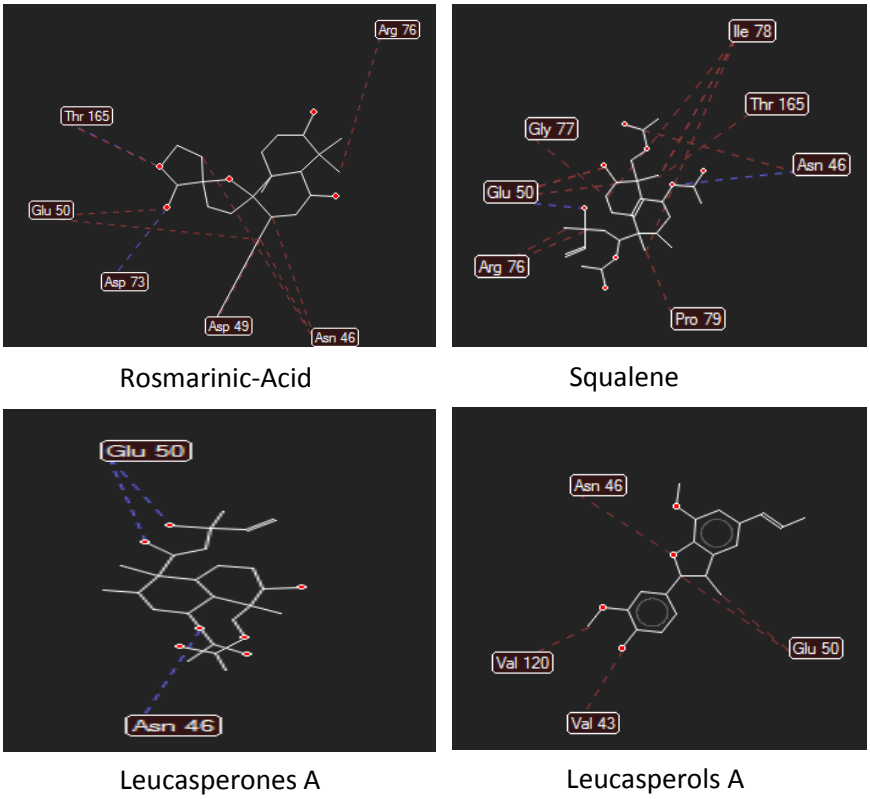


Figure 3: Binding interactions of selected molecules with DNA Gyrase-3

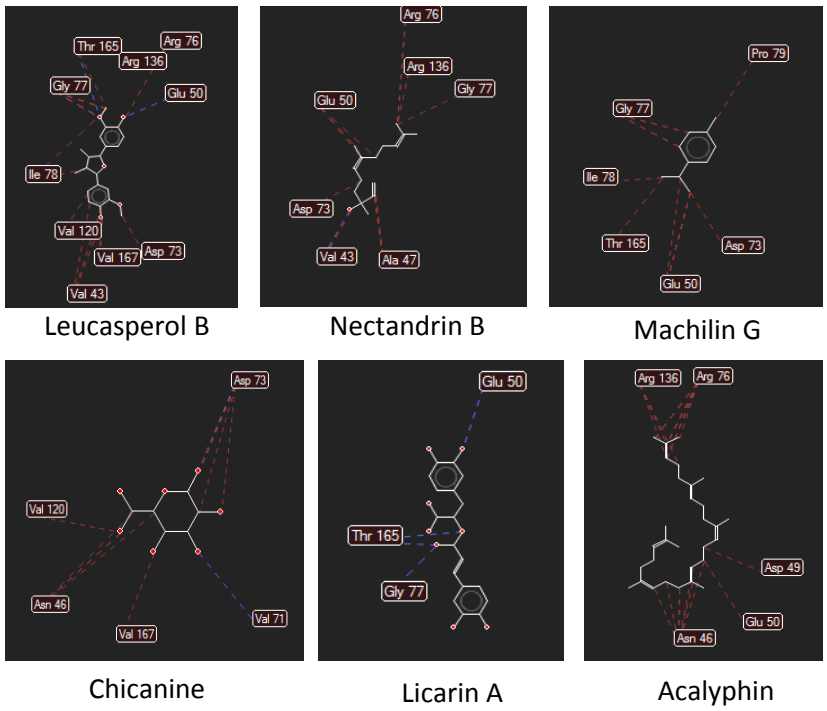


Figure 4: Binding interactions of selected molecules with DNA Gyrase-4

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